UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,424	02/27/2004	Srinivasa Nagalla		5692

7590 11/14/2008

SRINIVASA NAGALLA
30100 SW LAUREL ROAD
HILLSBORO, OR 97123

EXAMINER	
DEJONG, ERIC S	
ART UNIT	PAPER NUMBER
1631	
MAIL DATE	DELIVERY MODE
11/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,424	NAGALLA ET AL.	
	Examiner	Art Unit	
	ERIC S. DEJONG	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/01/2008 has been entered.

Claims 1-84 are pending and are currently under examination.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Objections

The objection to claims 81 under 37 CFR 1.75(c) as being in improper dependent form is withdrawn in view of amendments made to the instant claim.

Claim Rejections - 35 USC § 112

The rejection of claims 1-80 and 82-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of amendments made to the instant claims.

Claim Rejections - 35 USC § 101

The previous grounds of rejection for claims 1-80 and 82-84 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in view of the recent *en banc* decision by the CAFC regarding Bilski v. Warsaw (2008).

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-84 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The recent en banc decision regarding Bilski v. Warsaw (2008) set forth that a process is patent-eligible if (1) it is ties to a particular machine or apparatus or (2) it transforms a particular article into a different state or thing. The claimed process comprises the abstract/computational steps of calculating at least one mass-based alignment, interpreting mass differences of modification sites, and calculating at least one match score, and storing said score on a computer readable medium. In the instant case, the ultimate step of storing a score on computer readable media is considered an inconsequential post solution activity. The instant claims do not recite or inherently

involve any transformation of an article, therefore the Examiner must determine if the instant claims have a tie to a particular machine or apparatus. Instant claims 1-84 do not recite any limitation that ties the recited abstract process to any particular machine or apparatus. Therefore, the instant claims are directed to non-statutory subject matter as they wholly preempt the abstract process as set forth above.

Response to Arguments

Applicant's arguments with respect to claims rejected under 35 USC 101 have been considered but are moot in view of the new grounds of rejection set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12 and 63-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dancik et al. (J. Comp. Biol., 1999) in view of Pevzner et al. (see IDS filed 02/11/2005). The rejection of claims 81 are necessitated by amendments made to the instant claims.

The instant claims are drawn to a method for identifying a macromolecule having a sequence and sequence modification thereof from mass spectrometry data comprising providing at least one de novo sequence from mass spectroscopy data, calculating at least one mass-based alignment between each de novo sequence and a sequence in a sequence database, comparing molecular masses of fragments to molecular masses of sequence fragments contained in a sequence database, interpreting mass differences of modification sites between sequences in said database and at least one de novo sequence using a modification catalog, and calculating at least one match score for the mass-based alignment. Further claimed embodiments of the method comprises the additional steps of identifying sequences in the sequence database from mass-based alignments in response to the match score, and grouping identification of sequences from at least one de novo sequence into an identified macromolecule list that agrees with the mass.

Dancik et al. sets forth a review of de novo peptide and protein sequencing techniques via tandem mass spectrometry and the development of a software algorithm, SHERENGA (see Dancik et al., Abstract). Dancik et al. further sets forth that

SHERENGA addresses an art recognized need for the previously unsolved computation problems drawn to parameter learning, spectrum graphing, scoring schema, and sequencing algorithms (see Dancik et al., page 328, lines 24-45). Dancik et al. discloses methods for the identification of peptide and protein sequences using a tandem mass spectrometer capable of ionizing a mixture of peptides with different sequences and measuring their respective parent mass/charge ratios, selectively fragmenting each peptide into pieces and measuring the mass/charge ratios of the fragment ions (MS/MS spectra) and interpreting such MS/MS relies upon a data base searching (see Dancik et al., page 327, lines 1-11). Dancik et al. discloses that the automated SHERENGA further provides for improved *de novo* interpretation that automatically learns fragment ion types and intensity thresholds from a collection of test spectra generated from any type of mass spectrometer, wherein test data is used to construct optimal path scoring in the graph representations of MS/MS spectra and a ranked list of high scoring paths corresponding to potential sequences (see Dancik et al., Abstract and page 329, lines 1-27; page 330, lines 1 through page 333, line 9; and page 333, line 39 through page 336, line 5). Dancik et al. further disclose that peptides were obtained from in-gel or in-solution tryptic digestion of proteins isolated from yeast lysates, mouse plasma, and urine (see Dancik et al., page 338, lines 1-4). Dancik et al. further disclose an automated approach for scoring how well a candidate sequence "explains" a spectrum and then and selecting sequences that provide a best fit to a given spectrum. The disclosed scoring method relies upon an evaluation of probability that a given sequence P produces a given spectrum S via maximizing a probability function p(P,S) (see Dancik

et al., page 334, line 19 through page 336, line 5). Dancik et al. further provides results by the disclosed methods in Figures 5-9 (see Dancik et al. page 336, line 34 through page 337, line 20). Examples of interpretation with different quality are reflected by ambiguities in initial and/or terminal 1-3 amino acids (see page 336, line 34 through page 337, line 5). Dancik et al. further displays and labels mass objects relied upon to reflect different qualities of interpretation in Figure 10. To evaluate the performance of the disclosed de novo algorithms, Dancik et al. introduces the use of ladder difference metric between the predicted and actual sequences (see Dancik et al., page 337, lines 6-20).

While Dancik et al. sets forth the above discussed approaches to identifying sequences of molecules from mass spectrometry data, Dancik et al. does not fairly teach or suggest interpreting mass differences of modification between a sequence in a database and a de novo sequences that has been identified by mass based alignment as modifications in a modification catalog (see for example step (c) of instant claim 1).

Pevzner et al. sets forth methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry. Pevzner et al. further teach that the disclosed methods and algorithms address an art recognized need for algorithms that sort out reliable database hits from unreliable ones and identify mutated and modified peptides (see Pevzner et al., Abstract). Pevzner et al. further set forth that the disclosed approaches demonstrate advantages over known prior art methods and further demonstrate the use of a spectral alignment approach as a filter in a new database search algorithm that reliably identifies peptides differing by up to two

mutations/modifications from a peptide in a database (see Pevzner et al., Abstract). Figure 1 and Table 1 of Pevzner et al. list a plurality modified peptides used in the disclosed methods read on a modification catalog as instantly claimed. Further, Pevzner et al. rely upon MS/MS sequence methods to identify by mass based alignment to correlate sequence fragments to the modified peptides set forth in Figure 1 and Table 1 (see Pevzner et al., page 295, col. 2, line 43 through page 299, col. 1, line 15). Pevzner et al. further sets forth the application of spectral convolution of experimental and theoretical spectra that allow for the detection of mutations/modification without an exhaustive search (see Pevzner et al., page 292, col. 2, line 35 through page 294, col. 2, line 30). Figure 2 of Pevzner et al. further demonstrates the use of a set of differences matrixes, which are fairly interpreted as substitution matrixes, required to practice the spectral convolution procedures.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use the disclosed methods for the identification of sequences using a tandem mass spectrometry, as set forth by Dancik et al., in combination with the methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry, as set forth by Pevzner et al. One of skill in the art would be motivated to combine the teachings of Dancik et al. and Pevzner et al. because Pevzner et al. teaches that the disclosed methods and algorithms address an art recognized need for algorithms that sort out reliable database hits from unreliable ones and identify mutated

and modified peptides. One of ordinary skill in the art would further recognize that the combination of Dancik et al. and Pevzner et al. would yield expected results.

Claims 1-27 and 63-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dancik et al. in view of Pevzner et al., as applied to claims 1-12 and 63-84 above, and further in view of Mann et al. (see IDS filed 02/11/2005). The rejection of claim 81 is necessitated by amendments made to the instant claims.

The instant claims recite further embodiments comprising the steps of identifying a sequence in the sequence database with a tag match and generating a mass-based alignment between a de novo sequence and a sequence in the sequence database.

Dancik et al. in view Pevzner et al. provide for the above discussed methods of identifying sequences using a tandem mass spectrometry, as set forth by Dancik et al., in combination with the methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry, as set forth by Pevzner et al. However, neither Dancik et al. nor Pevzner et al. fairly teach or suggest identifying a sequence in a sequence database with a tag match (see for example, step (a) of instant claim 13).

Mann et al. demonstrate an approach to the identification of mass spectrometrically fragmented peptides (see Mann et al., Abstract). Mann et al. set forth that the disclosed methods as a means for interpreting complex tandem mass spectra by use of searching by peptide sequence tags (see Mann et al., page 4390, col. 2, lines 1-32). Mann et al. further demonstrate that MS/MS data can be relied upon for peptide

identification with tags as short as two amino acids that can further be located in the presence of posttranscriptional modification or a sequence difference between the measured peptide and the peptide database (see especially Mann et al., page 4390, col. 2, lines 23-31 and page 4393, col. 1, line 25 through page 4397, col. 2, line 3).

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use the disclosed methods for the identification of sequences using a tandem mass spectrometry, as set forth by Dancik et al., in combination with the methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry, as set forth by Pevzner et al., and in further combination with searching methods that rely on peptide sequence tags, as set forth by Mann et al. One of skill in the art would be motivated to combine the teachings of Dencik et al., Pevzner et al., and Mann et al., because Mann et al. teaches that the error tolerance of the peptide sequence tag approach is very high and is crucial in cases where predicted mass peptides is likely to be wrong (see especially, Mann et al., page 4398, col. 1, lines 22-37). One of ordinary skill in the art would further recognize that the combination of Dancik et al., Pevzner et al., and Mann et al. would yield expected results.

Claims 1-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dancik et al. in view of Pevzner et al. in view of Mann et al. as applied to claims 1-27 and 63-84 above, and further in view of Bader (Bioinformatics, 2003). The rejection of claim 81 necessitated by amendments made to the instant claims.

The instant claims recite further embodiments comprising generating mass-based alignment using a breadth-first search (see for example instant claim 28).

Dancik et al. in view Pevzner et al. in view of Mann et al. provide for the above discussed methods of identifying sequences using a tandem mass spectrometry, as set forth by Dancik et al., in combination with the methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry, as set forth by Pevzner et al., and in further combination with searching methods that rely on peptide sequence tags, as set forth by Mann et al. However, neither Dancik et al., Pevzner et al., nor Mann et al. fairly teach or suggest generating mass-based alignment using a breadth-first search.

Bader sets forth methods related to extracting relevant complexes and pathways from high-throughput proteomics data sets to identify and extract networks are that essential to the art recognized problem of building pathways starting from known proteins of interest (see Bader, page 1869, col. 1, lines 1-10). Bader discloses the developed of an efficient algorithm, SEEDY, that extracts biologically relevant biological networks from protein–protein interaction data, building out from selected seed proteins. The algorithm relies on a previous study establishing statistical confidence levels for interactions generated by two-hybrid screens and inferred from mass spectrometric

identification of protein complexes (see Bader, page 1869, col. 1, lines 11-25). Bader further discloses the evaluation of the disclosed algorithm by use of a breadth-first outward search based on an outward traversal of a protein interaction network (see Bader, page 1870, col. 2, lines 5-22).

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use the disclosed methods for the identification of sequences using a tandem mass spectrometry, as set forth by Dancik et al., in combination with the methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry, as set forth by Pevzner et al., in combination with searching methods that rely on peptide sequence tags, as set forth by Mann et al., and in further combination with the use of a breadth-first outward search based on an outward traversal of a protein interaction network, as set forth by Bader. One of skill in the art would be motivated to combine the teachings of Dencik et al., Pevzner et al., and Mann et al., because Bader teaches that the disclosed breadth-first outward search is applicable to the analysis of an algorithms inferred from mass spectrometric identification of protein complexes. One of ordinary skill in the art would further recognize that the combination of Dancik et al., Pevzner et al., Mann et al. and Bader et al. would yield expected results.

Response to Arguments

Applicant's arguments filed 08/01/2008 have been fully considered but they are not persuasive.

In regards to the rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Dancik et al. in view of Pevzner et al., applicants argue that Dancik et al. in view of Pevzner et al. does not teach interpreting mass differences between the sequence in the sequence database and the de novo sequence using a modification catalog.

it is reiterated from the instant rejection that Pevzner et al. is relied upon for teaching methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry. Pevzner et al. further teaches the use of a spectral alignment approach as a filter in a new database search algorithm that reliably identifies peptides differing by up to two mutations/modifications from a peptide in a database. The listings of a plurality modified peptides used in the disclosed methods (see Figure 1 and Table 1 of Pevzner et al.) read on the use of a modification catalog to identify sequence modifications as instantly claimed. Neither the instant claims nor the instant specification provide a limiting definition for the contents of "a modification catalogue" that would exclude the listings of a plurality modified peptides as taught by Pevzner et al. Therefore applicants arguments are not found persuasive.

Applicants further argue that Dancik et al. in view of Pevzner et al. does not teach grouping identifications of sequences in the sequence database from at least one

de novo sequence into an identified macromolecule list that agrees with the de novo sequencing results.

In response, Dancik et al. is relied upon in the instant rejection for teaching a scoring method that relies upon an evaluation of probability (see Dancik et al., page 334, line 19 through page 336, line 5) and disclosing a listing grouped of identified sequences resulting from the disclosed mass based alignment methodology (see Figures 8 and 9 of Dancik et al.), which reads on grouping identifications of sequences into an identified macromolecule list as instantly claimed. Therefore applicants arguments are not found persuasive.

Applicants further argue that the present invention claims a method that is capable of characterizing a greater number of specific isobaric equivalences, thus meeting a long felt need.

In response, applicants argument that the instant claims meet a long felt need amount to an assertion as no affidavit or evidence has been submitted as support of said assertion. Applicants argument alone is not sufficient to demonstrate the secondary considerations such as meeting a long felt need in the art.

Applicants further argue that Pevzner et al. specifically teaches away from the claimed invention. Applicants further cite examples 3, and 6 of the instant specification as support.

In response, applicants reliance of exemplary embodiments from the specification fail to demonstrate how the language of the instant claims differentiates the claimed invention from that of set forth in the prior art. Applicants are reminded that while the instant claims are interpreted in light of the disclosure, limitations from the instant specification are not imported into the claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. DEJONG whose telephone number is (571)272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S DeJong/
Primary Examiner, Art Unit 1631